Vitamin D and multiple health outcomes

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RESEARCH

Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials

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Abstract

Objective To evaluate the breadth, validity, and presence of biases of the associations of vitamin D with diverse outcomes.

Design Umbrella review of the evidence across systematic reviews and meta-analyses of observational studies of plasma 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D concentrations and randomised controlled trials of vitamin D supplementation.

Data sources Medline, Embase, and screening of citations and references.

Eligibility criteria Three types of studies were eligible for the umbrella review: systematic reviews and meta-analyses that examined observational associations between circulating vitamin D concentrations and any clinical outcome; and meta-analyses of randomised controlled trials assessing supplementation with vitamin D or active compounds (both established and newer compounds of vitamin D).

Results 107 systematic literature reviews and 74 meta-analyses of observational studies of plasma vitamin D concentrations and 87 meta-analyses of randomised controlled trials of vitamin D supplementation were identified. The relation between vitamin D and 137 outcomes has been explored, covering a wide range of skeletal, malignant, cardiovascular, autoimmune, infectious, metabolic, and other diseases. Ten outcomes were examined by both meta-analyses of observational studies and meta-analyses of randomised controlled trials, but the direction of the effect and level of statistical significance was concordant only for birth weight (maternal vitamin D status or supplementation). On the basis of the available evidence, an association between vitamin D concentrations and birth weight, dental caries in children, maternal vitamin D concentrations at term, and parathyroid hormone concentrations in patients with chronic kidney disease requiring dialysis is probable, but further studies and better designed trials are needed to draw firmer conclusions. In contrast to previous reports, evidence does not support the argument that vitamin D only supplementation increases bone mineral density or reduces the risk of fractures or falls in older people.

Conclusions Despite a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable.

Introduction

The associations between vitamin D concentrations and various conditions and diseases have been assessed in a large and rapidly expanding literature. In addition to observational studies, numerous randomised trials have examined the effect of vitamin D supplementation on a range of outcomes. Historically, vitamin D had been linked to skeletal disease including calcium, phosphorus, and bone metabolism,[1 2] osteoporosis,[3] fractures,[4 5] muscle strength,[6] and falls.[7] In the 2000s, growing scientific attention turned to non-skeletal chronic diseases as vitamin D deficiency was linked to cancer,[8] cardiovascular diseases,[9 10] metabolic disorders,[11] infectious diseases,[12] and autoimmune diseases,[13-15] as well as mortality.[16] If causal, these associations might be of great importance for public health, as vitamin D deficiency has been found to be highly prevalent in populations residing at high latitudes or leading an indoors oriented lifestyle.[17] However, the composite literature is often confusing and has led to heated debates about the optimal concentrations of vitamin D and related guidelines for supplementation.[18-20]

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To provide an overview of the breadth and validity of the claimed associations of vitamin D with diverse outcomes, we have done an umbrella review of the evidence across existing systematic reviews and meta-analyses. We aimed to do a comprehensive evaluation of systematic reviews and meta-analyses of observational studies that examined associations of vitamin D concentrations with a range of clinical outcomes, as well as meta-analyses of randomised controlled trials of vitamin D supplementation. We also compared the findings of the observational studies with those from meta-analyses of randomised controlled trials of vitamin D supplementation, whenever these could be juxtaposed. We sought to summarise the health outcomes that have been associated with vitamin D concentrations, evaluate whether evidence exists of biases in this literature, identify health outcomes without evidence of biases, and examine the consistency of inferences from the meta-analyses of observational studies and of randomised controlled trials.

Methods

Structure of umbrella review

An umbrella review systematically collects and evaluates information from multiple systematic reviews and meta-analyses on all clinical outcomes for which these have been performed.[21] Here, for evidence on observational associations between vitamin D concentrations and any health outcome, we sought to collect information from systematic reviews regardless of whether they also included quantitative syntheses (meta-analyses). Given the very large heterogeneity that may be encountered in observational studies, often meta-analysis may not be done in systematic reviews of observational studies, whereas this problem occurs much less frequently in systematic reviews of randomised controlled trials, for which meta-analysis is the norm, especially when interventions are drugs or vitamins.[22] Where available, we also evaluated in more depth the quantitative results of the meta-analyses of observational associations and potential hints of bias in these meta-analyses.[23-25] For evidence on randomised controlled trials of vitamin D supplementation, we considered only formal quantitative meta-analyses. We compared results from meta-analyses of observational studies and randomised controlled trials, whenever data were available for the same outcome.

Search strategy

Two reviewers (IT, ET) searched Medline and Embase in duplicate, using the search algorithm in supplementary table A, from inception to 11 October 2013 (last update) and limited the search to humans and English language, as the overwhelming majority of review studies are published in English language, peer reviewed journals. Any discrepancies were resolved with discussion. We firstly perused the title and abstract of each of these citations and then retrieved potentially eligible articles for perusal in full text.

Eligibility criteria and appraisal of included studies

Three types of studies were eligible for the umbrella review: observational associations between circulating vitamin D concentrations and any clinical outcome examined in systematic reviews, meta-analyses, or both; and meta-analyses of randomised controlled trials assessing supplementation of vitamin D or active compounds (both established and newer compounds of vitamin D). We excluded studies that examined genetic polymorphisms related to vitamin D metabolism (for example, vitamin D receptor); systematic reviews and meta-analyses of observational studies assessing dietary or supplementary vitamin D intake or ultraviolet B exposure; studies that had vitamin D status as the outcome; studies that investigated the prevalence of vitamin D deficiency in certain disease populations; and meta-analyses of randomised controlled trials in which the treatment arm combined vitamin D with calcium or other vitamins or compounds versus placebo. When the treatment arm and control arm included the same additional compound (for example vitamin D and calcium versus calcium), we included the meta-analysis in the review. We included meta-analyses regardless of the baseline characteristics (clinical setting or age) of the examined populations. If an article presented separate meta-analyses on more than one eligible outcome or type of clinical setting, we assessed those separately.

Appraisal of individual component studies was beyond the scope of this umbrella review. This was the aim of the original systematic reviews and meta-analyses, which should include an appraisal of studies' quality. In respect to the selected systematic reviews and meta-analyses, we used methods that captured essential features of the quality of the evidence, and these are described in detail in the data analysis section.

Data extraction

Three investigators (ET, IT, LZ) extracted data independently. From each eligible systematic review or meta-analysis, we abstracted the PubMed ID, first author, journal, year of publication, vitamin D biomarker, population, and outcome examined. From each systematic review of observational studies, we recorded a statement summarising the authors' main interpretations of their findings. From each meta-analysis of observational studies or randomised controlled trials, we further abstracted data on the studies included in the analysis: the study specific relative risk estimates (risk ratio, odds ratio, hazard ratio, or incident risk ratio, as reported by the authors of the meta-analysis), along with the corresponding confidence intervals and the number of cases and controls for each study.

We categorised outcomes into the following categories: autoimmune diseases, cancer outcomes, cardiovascular outcomes, cognitive disorders, infectious diseases, metabolic disorders, neonatal/infant/child related outcomes, pregnancy related outcomes, skeletal outcomes (including falls), and "other" outcomes (supplementary table B).

Data analysis

We carried out descriptive analysis for systematic reviews. We categorised the conclusions of each systematic review for the association of vitamin D and the outcome of interest in one of the following four categories: definite association, suggestive (possible) association, no association, or inconclusive (insufficient) evidence. Whenever more than one systematic review had been performed on the same outcome, we examined whether the main reported conclusions were concordant. We retained the most recent systematic review for further analyses.

When we identified more than one meta-analysis of observational studies examining the association between a given vitamin D biomarker and outcome pair in the same clinical setting, we examined the conclusions for concordance regarding the direction, level of statistical significance (at $P \leq 0.05$), and magnitude (overlapping confidence interval) of the association. Then, we again retained only the most recent meta-analysis with eligible data for further statistical analysis. We estimated the summary effect size and its confidence interval by using random

effects models and calculated the I^2 and its confidence interval metric for heterogeneity for each eligible meta-analysis that reported the effect sizes, number of cases, and total number of participants of the component studies.[26 27] We used the regression asymmetry test to test for small study effects.[28] We also applied the excess significance test, which evaluates whether the observed number of studies with statistically significant results ("positive" studies) differs from the expected number of positive studies, by using a χ^2 test.[29-31] The expected number of positive studies for each meta-analysis is calculated by the sum of the statistical power estimates for each component study. We estimated the power of each study for an effect equal to the effect of the largest study (study with the smallest variance), as previously described.[32] We used appropriate equations to estimate the power, on the basis of whether the largest study reported a hazard ratio or an odds ratio.[33 34] If the type of the metric was a standardised mean difference, we transformed this to an odds ratio before using it in the analysis.

Eight meta-analyses presented in five papers were not included in the excess significance bias analysis either because individual study data was unavailable[35 36] or because it reported the logarithm of geometric mean ratio,[37] the weighted mean difference,[36] or the Fisher's z score.[38] Both the small study and excess significance tests were considered significant at P<0.10, as previously proposed.[23]

We specifically identified outcomes for which meta-analyses of observational studies showed nominally significant associations (at P≤0.05), did not have large between study heterogeneity, were based on evidence from more than 500 cases (or more than 5000 total participants if the type of metric was continuous), and showed no evidence of small study effects or excess significance. We also noted how many would satisfy the same criteria but with P≤0.001, which has been considered to be a more appropriate threshold of statistical significance to reduce false positives.[39-41]

When we identified more than one meta-analysis of randomised controlled trials examining the relation between vitamin D supplementation and outcome pair in the same clinical setting, we examined the conclusions for concordance regarding the direction, level of statistical significance (at P≤0.05), and magnitude (overlapping confidence interval) of the association.

When meta-analyses for the same outcome existed both for association studies of vitamin D concentrations and for randomised controlled trials of vitamin D supplementation, we compared their results in terms of whether a nominally statistically significant effect had been described (P≤0.05) and whether the effect estimate was in the same direction. We did not compare the magnitude of the effect sizes between circulating vitamin D concentrations and vitamin D supplementation, as these are difficult to translate to the same vitamin D concentration/treatment contrasts. Whenever no meta-analysis of observational studies existed for an outcome examined by a meta-analysis of randomised controlled trials, we compared the main results with the results of a systematic review of observational studies, if available. Finally, we applied a set of criteria to conclude whether the evidence for a given outcome was definite, probable, suggestive, not conclusive, or unlikely (see box).

We used Stata version 12.1 for statistical analyses. P values were two tailed.

Results

Overall, 1256 articles searched yielded 107 systematic reviews without meta-analyses (presented in 24 papers)[36 42-64] and 74 meta-analyses (47 papers)[11 35-38 52 65-105] of observational studies that investigated associations with circulating vitamin D concentrations. In addition, we identified and included 87 meta-analyses (32 papers)[5 7 37 52 61 70 106-131] of randomised controlled trials of vitamin D supplementation (fig 1⇓; supplementary tables C-E). Across all three study types, results on 137 unique outcomes were reported (fig 2⇓; supplementary table B).

Vitamin D concentrations and health outcomes: systematic reviews of observational studies

The median number of observational studies included in the systematic reviews was four (range 1-28) (supplementary table C). Among the 107 identified systematic reviews, 76 unique ones were presented in 21 papers (supplementary table B),[36 43-49 52-64] whereas more than one systematic review existed for 24 outcomes (in 15 of which the authors reached the same qualitative conclusion; supplementary table C).

For only six (8%) of the 76 unique outcomes, the systematic reviews concluded that a definite association existed (supplementary tables B and F). These were rheumatoid arthritis activity, colorectal cancer, hypertension in children, bacterial vaginosis in pregnant women, falls in older people, and rickets in children; for all these outcomes, higher concentrations of vitamin D were associated with lower risk. Conversely, for 10 (13%) outcomes, the authors concluded that no association existed between the examined outcome and vitamin D status. For 60 of the 76 unique outcomes, the systematic reviews did not reach a firm, unequivocal conclusion: for 43 (57%) authors reported that the reviewed data were inconclusive or insufficient to draw any firm conclusions, and 17 (22%) found that an inverse association was possible or suggestive. No systematic reviews concluded that a definite or suggestive association existed for increased risk with higher concentrations of vitamin D.

Vitamin D concentrations and health outcomes: meta-analyses of observational studies

We identified 74 meta-analyses of observational studies (supplementary table D). Among these, 48 unique meta-analyses were presented in 28 papers (fig 1⇓; supplementary table G).[35-38 66 68 71 74 76 78 79 82-84 86 88 89 91 95 96 98-105] Forty three meta-analyses examined the link between vitamin D and outcome by using 25-hydroxyvitamin D and five by using 1,25-dihydroxyvitamin D. All meta-analyses reported estimates adjusted for a wide variety of other covariates. Meta-analyses examined a very wide range of outcomes including cancers (n=20), cardiovascular diseases (n=8), cognitive disorders (n=4), metabolic disorders (n=4), neonatal/infant/child related outcomes (n=4), skeletal diseases (n=3), pregnancy related outcomes (n=2), infectious disease (n=1), or other outcomes (n=2) (supplementary table G). The median number of studies included was seven (range 2-37), the median number of participants was 5905 (39-82 982), and the median number of events was 1289 (18-15 447). Overall, 30 (63%) of the 48 meta-analyses of observational studies reported a nominally statistically significant summary result (tables 1⇓ and 2⇓). Figure 3⇓ shows a forest plot with the summary effects of all the non-overlapping meta-analyses of observational studies (for binary outcomes).

We found more than one published meta-analysis for 11 outcomes: Alzheimer's disease (n=2 meta-analyses), breast cancer (n=6), colorectal adenoma (n=3), colorectal cancer (n=7),

Criteria for evidence categories

Convincing—Evidence existed from both observational studies and randomised controlled trials (RCTs), and association/effect was of the same direction, statistically significant at P≤0.001, and free from bias

Probable—Evidence existed from both observational studies and RCTs, and association/effect was of the same direction and statistically significant at P≤0.001, but excess significance could not be tested; or evidence existed from RCTs and effect was statistically significant at P≤0.001 and with no contrary results from observational data (that is, systematic reviews, if any exist, are also definitive or suggestive and meta-analyses of observational studies, if any exist, are in the same direction)

Suggestive—Evidence from RCTs with an effect at 0.001≤ P≤0.05 and with no contrary results from observational data (same as above); or evidence from meta-analyses of observational studies showing an association at P≤0.001, with no contrary results from randomised data (that is, meta-analysis of RCTs, if present, have effects in the same direction) and, if it could be tested, no evidence of small study effects (P≥0.10), not very large heterogeneity (I^2≤75%), no evidence for excess significance, based on cumulative evidence of more than 500 disease events (or more than 5000 total participants if type of metric was continuous)

No conclusion—Not enough evidence from observational studies or RCTs to draw conclusion

Substantial effect unlikely—Evidence from observational studies or RCTs enough to conclude that a substantial effect is unlikely based on the magnitude and the significance level

cardiovascular diseases (n=3), gestational diabetes (n=2), hypertension (n=3), prostate cancer (n=4), stroke (n=2), type 2 diabetes (n=3), and prevalence of type 2 diabetes (n=2). For all the outcomes, agreement existed between the meta-analyses on the direction, magnitude, and statistical significance of the association (supplementary table H).

Summary effects, heterogeneity, and bias tests for meta-analyses of observational associations

Of the 48 non-overlapping meta-analyses of observational studies, the largest study had statistically significant results in 21 (44%) meta-analyses (supplementary figure A). The largest study's result was more conservative than the summary result in 20 (42%) meta-analyses. Fifteen (31%) meta-analyses had large heterogeneity (I^2>50%), and seven (15%) had very large heterogeneity (I^2>75%). Evidence for significant small study effects was noted in three meta-analyses (breast cancer, all cause mortality, and cardiovascular disease mortality) (tables 1⇓ and 2⇓). Evidence for statistically significant excess significance bias was seen for three outcomes (sporadic colorectal adenoma recurrence, Alzheimer's disease, and fractures; supplementary table I).

Significant observational associations without hints of bias

Of the 48 meta-analyses, 18 (38%) had nominally statistically significant summary associations according to random effects calculations and had no evidence of small study effects (P≥0.10), not very large heterogeneity (I^2≤75%), and no evidence for excess significance (tables 1⇓ and 2⇓). Overall, 12 of these 18 associations were based on cumulative evidence of more than 500 disease events (or more than 5000 total participants if the type of metric was continuous) and also had P≤0.001 for the association. These included vitamin D associations with one cancer (colorectal cancer), five cardiovascular (cardiovascular disease, prevalence of cardiovascular disease, hypertension, ischaemic stroke, and stroke), two cognitive (cognition and depression (cohort studies)), two metabolic (prevalence of metabolic syndrome and type 2 diabetes), one neonatal/infant/child related (small for gestational age), and one pregnancy related outcome (gestational diabetes). Across these 12 associations, the relative risk of the highest versus the lowest category had a median of 0.63 (interquartile range 0.52-0.67).

Meta-analyses of randomised controlled trials of vitamin D supplementation

We identified 87 meta-analyses of randomised controlled trials of vitamin D supplementation (supplementary table E). Among these, 57 non-overlapping meta-analyses were presented in 19 papers,[5 61 107 108 110-112 114 115 118-121 123 125 127 128 130 131] including 21 (37%) in skeletal diseases, seven (12%) in metabolic disorders, four (7%) in neonatal/infant/child related outcomes, three (5%) in cardiovascular diseases, three (5%) in pregnancy related outcomes, and 18 (32%) in other outcomes. The median number of studies included was four (range 2-38), and the median number of participants was 446 (38-25 016) (tables 3⇓ and 4⇓). Overall, 13 (23%) of the 57 meta-analyses of randomised controlled trials reported a nominally statistically significant summary result, and these were related to the following outcomes: total cholesterol concentrations, birth weight, head circumference at birth, maternal vitamin D concentrations at term, balance sway, femoral neck bone mineral density, muscle strength, non-vertebral fractures, rate of falls, dental caries in children, parathyroid hormone concentrations in patients with chronic kidney disease (requiring or not requiring dialysis), and risk of hypercalcaemia in patients with chronic kidney disease not requiring dialysis (tables 3⇓ and 4⇓). Figure 4⇓ shows a forest plot with the summary effects of all the non-overlapping meta-analyses of randomised controlled trials (for binary outcomes).

We found more than one meta-analysis of randomised controlled trials for 10 outcomes: cardiovascular disease (n=2 meta-analyses), diastolic blood pressure (n=3), systolic blood pressure (n=3), birth weight (n=3), falls (n=11), fractures (n=5), hip fractures (n=4), non-vertebral fractures (n=2), rate of falls (n=3), and mortality (n=5). For half of the outcomes, agreement existed between the meta-analyses on the direction, magnitude, and statistical significance of the effect. Only one of the overlapping meta-analyses reported a statistically significant effect for diastolic blood pressure, birth weight, and non-vertebral fractures. Eleven meta-analyses examined risk of falling, and differences existed in both the magnitude and the statistical significance of the effect but not in the direction of the effect. Finally, three meta-analyses examined rate of falls, and differences existed in the direction, magnitude, and statistical significance of the effect (supplementary table J).

Comparison of findings from observational studies and clinical trials

One hundred and twenty three (90%) outcomes were examined only by syntheses of observational evidence (n=84) or only by meta-analyses of randomised evidence (n=39), so we could not compare observational and randomised evidence.

Ten (7%) outcomes were examined by both meta-analyses of observational studies and meta-analyses of randomised controlled trials: cardiovascular disease, hypertension, birth weight, birth length, head circumference at birth, small for gestational age birth, mortality in patients with chronic kidney

disease, all cause mortality, fractures, and hip fractures (table 5⇓). The direction of the association/effect and level of statistical significance was concordant only for birth weight, but this outcome could not be tested for hints of bias in the meta-analysis of observational studies (owing to lack of the individual data). The direction of the association/effect but not the level of statistical significance was concordant in six outcomes (cardiovascular disease, hypertension, birth length, head circumference small for gestational age births, and all cause mortality), but only two of them (cardiovascular disease and hypertension) could be tested and were found to be free from hint of bias and of low heterogeneity in the meta-analyses of observational studies. For mortality in chronic kidney disease patients, fractures in older populations, and hip fractures, both the direction and the level of significance of the association/effect were not concordant.

Finally, four (3%) outcomes were examined by meta-analyses of randomised controlled trials and systematic reviews of observational studies without a formal meta-analysis (supplementary table B). These included falls, for which systematic reviews concluded that a definite association existed whereas meta-analyses of randomised controlled trials reported a non-statistically significant effect, and length of gestation and bone mineral density in adults and in children, for which the systematic reviews concluded that a suggestive association existed whereas meta-analyses of randomised controlled trials reported a non-statistically significant effect.

Discussion

Our umbrella review identified 107 systematic literature reviews and 74 meta-analyses of observational studies of plasma vitamin D concentrations and 87 meta-analyses of randomised controlled trials of vitamin D supplementation. The role of vitamin D has been explored in relation to an impressive number of outcomes (137 in total), covering a wide range of diseases, including among others skeletal, malignant, cardiovascular, autoimmune, infectious, and metabolic diseases. We identified a gap in the literature concerning autoimmune disease outcomes, as we found no formal meta-analyses of either observational studies or randomised controlled trials and these were examined only by systematic reviews. Furthermore, cancer, cognitive, and infectious disease outcomes were examined only in observational studies of plasma vitamin D concentrations (either systematic reviews or formal meta-analyses), and we found no meta-analyses of randomised controlled trials of vitamin D supplementation. Comparisons of syntheses of observational versus randomised evidence were possible for only 14 of the 137 outcomes. Largely, this unevenness in observational versus randomised evidence may reflect the low frequency of many of these outcomes, which would be difficult to study conclusively with randomised trials.

Most of the associations that give signals of nominal significance for diverse outcomes are subject to the caveats that generally accompany evidence from observational studies: many of them may be false positives, and very few, if any, may translate to effective interventions when tested in randomised trials. Even meta-analyses of randomised trials may not be conclusive, especially when based on limited sample size and weak levels of statistical significance. On the basis of the results of this umbrella review (table 6⇓), highly convincing evidence of a clear role of vitamin D with highly significant results in both randomised and observational evidence does not exist for any outcome. Vitamin D supplementation is probably linked to a decrease in dental caries in children and in parathyroid hormone concentrations in patients with chronic kidney disease requiring dialysis and to an increase in maternal vitamin D concentrations at term and in birth weight. Suggestive evidence exists for a correlation between high vitamin D concentrations and low risk of colorectal cancer, non-vertebral fractures, cardiovascular disease, prevalence of cardiovascular disease, hypertension, ischaemic stroke, stroke, cognition, depression, high body mass index, prevalence of metabolic syndrome, type 2 diabetes, head circumference at birth, small for gestational age birth, and gestational diabetes mellitus; reduced levels of balance sway, alkaline phosphatase concentrations in chronic kidney disease patients requiring dialysis, and parathyroid hormone concentrations in chronic kidney disease patients not requiring dialysis; and increased levels of low density lipoprotein, bone mineral density in femoral neck, and muscle strength. On the other hand, suggestive evidence exists that high vitamin D concentrations are linked to an increased rate of falls and risk of hypercalcaemia in chronic kidney disease patients not requiring dialysis.

Most (30/48) of the meta-analyses of observational studies reported a nominally statistically significant result. However, meta-analyses of randomised controlled trials reported a nominally statistically significant summary result for only 13 of the 57 outcomes, and the confidence intervals of the estimates were generally wider than the confidence intervals of the meta-analyses of observational studies. This may reflect lower power in meta-analyses of randomised controlled trials (due to fewer included studies and participants) and a different range of examined outcomes, or it may in part be due to the more conservative results in randomised controlled trials than in observational studies. The highly promising results identified from most of the meta-analyses of observational studies were either not tested or not replicated in meta-analyses of randomised controlled trials. In most cases, this was not only a matter of statistical significance but in addition the meta-analysis effect estimates were close to null for the randomised controlled trials.

Genuine differences between these two designs might be due to confounding or biases that operate in observational studies. Alternatively, difficulties in relation to randomised controlled trials of vitamin D supplementation may affect reliability of findings. “Typical” difficulties concern disentangling the effects of multiple compounds when administered simultaneously and assuring an appropriate follow-up period: although this would have been assured for primary outcomes, the follow-up time may be inadequate to allow differences in disease occurrence to become apparent for secondary outcomes. Similarly, an inappropriately low dose or short duration of vitamin D supplementation in the randomised controlled trials might be inadequate to raise the body’s vitamin D concentrations enough to show a difference between the arms of a trial. Differences in vitamin D concentrations achieved following supplementation can be much smaller than naturally occurring variation in the general population.[132] Moreover, large differences in baseline plasma concentrations of 25-hydroxyvitamin D in different populations could interfere with the effect of the supplementation. Finally, contamination with private use of vitamin D might also further dilute any definite associations.[133]

Strengths and weaknesses of study and in relation to other studies

This umbrella review provides a comprehensive summary of the published literature in relation to the role of vitamin D in human diseases and health related traits. Beyond summarising the findings for a wide range of outcomes, we explored the extent of bias and heterogeneity in the observational vitamin D

literature. As in all literature reviews, the quality is directly related to the quality of the included studies. Furthermore, some health related outcomes were poorly covered, and we have flagged this gap. Exploring the relation between vitamin D supplementation dose and effect size reported in randomised controlled trials was beyond the scope of this review. Similarly, we could not evaluate the effect of the different choices of comparison groups (for example, thirds, quarters, fifths) or of varying vitamin D distributions and median differences of the component observational studies.

We decided to exclude observational meta-analyses of vitamin D supplementation and include only meta-analyses of randomised controlled trials in relation to vitamin D supplementation. Meta-analyses of randomised controlled trials are subject to considerably less bias than are those of observational studies and are therefore selected as the standard against which observational meta-analyses of vitamin D concentrations are compared. Meta-analyses of observational studies of supplement intake are unlikely to be more reliable than the meta-analyses of observational studies of associations with vitamin D concentrations, so one could not really use them as a gold standard for assessing how the bias, size, or heterogeneity mapping performs.

We did not identify prominent bias in the observational plasma vitamin D literature, with respect to either the excess significance test (which evaluates whether the results of single studies are over-optimistic compared with the results of the largest study) or the small study effects test (which evaluates whether small studies are consistently more positive or negative than larger studies). This differs from findings of other empirical evaluations of biomarker studies.[23-25] This is because large studies in our review had relatively similar results to other studies and to the summary meta-analysis effect. This might mean that the same confounding or other biases affected all studies regardless of sample size. Other types of confounding or biases, such as reverse causality, might operate in this field, and these tests are not designed to probe this.

As we were preparing our review for submission, a relevant overview of observational studies and randomised controlled trials of vitamin D status or supplementation and ill health was published online.[132] Eligible papers included prospective cohort studies and randomised controlled trials on chronic diseases (excluding skeletal diseases) in adults and were identified through a search in PubMed and Embase from inception to 31 December 2012. The authors identified 82 prospective cohort studies, 84 randomised controlled trials, 20 meta-analyses of 208 prospective studies, and eight meta-analyses of 88 randomised controlled trials. Similarly to our findings, this overview identified a discrepancy between findings of observational studies and of randomised controlled trials, with most supplementation trials not showing an effect of vitamin D on disease occurrence, and the authors concluded that low vitamin D status is more likely to be a marker of ill health than a cause of disease. The results of this overview were similar to ours, but our review is more comprehensive in terms of the number and range of outcomes covered and different regarding the included studies (we included systematic reviews and meta-analyses rather than original studies), the underlying population (we did not restrict our analysis to adults or particular clinical settings), and the statistical analyses performed (including bias tests).

Possible explanations and implications for clinicians and policy makers

No universal consensus exists on the optimal vitamin D intake or the optimal plasma concentrations of 25-hydroxyvitamin D. The Institute of Medicine issued a report in 2011 stating that 25-hydroxyvitamin D concentrations of 50 nmol/L are adequate and suggested that these concentrations can be achieved by 600 IU of vitamin D per day.[20] Furthermore, vitamin D supplementation has been long thought to protect against osteoporosis and consequently to reduce the risk and number of fractures, so large numbers of older adults use vitamin D supplements.[134] That nearly half of the meta-analyses of randomised controlled trials were related to skeletal diseases is not surprising. Several randomised controlled trials have identified a protective effect of vitamin D supplementation (with or without co-administration of calcium) against fractures,[135 136] but trials that examined vitamin D only supplementation failed to replicate these findings.[107] Similarly, a very recent meta-analysis of randomised controlled trials on bone mineral density failed to show a definite association and concluded that widespread use of vitamin D supplementation for prevention of osteoporosis is not supported by the evidence,[131] a fact that is also verified by the findings of our review. Vitamin D might not be as essential as previously thought in maintaining bone mineral density. Similar are our findings for falls, with the results of two recent Cochrane reviews failing to find a protective effect of vitamin D only supplementation on the risk or rate of falling in older adults (both in care facilities or hospitals and in the community).[111 115]

The lack of convincing associations and the relative dearth of probable associations (table 6⇓) suggest that evidence for benefits that may be reaped from population-wide vitamin D supplementation is weak. Probable associations, where highly significant effects appear in randomised trials, hold the most promise for clinical translation, but they pertain to specific populations (children, pregnant women, patients with chronic kidney disease), and even in these cases the evidence is not sufficient to make universal recommendations about daily intake. Optimal vitamin D intake/concentration may not be the same for all outcomes.[137] In addition, the absorption/metabolism of vitamin D differs among individuals; in practice, this means that the same supplementation dose is not going to have a stable effect on plasma vitamin D concentration, introducing yet another source of variability. Moreover, individual characteristics (such as body mass index or disease) will further modify final concentrations in circulation. In this regard, current recommendations on daily supplementation of vitamin D are largely expert driven, rather than evidence based,[20] and this may be the reason why they have generated so much debate. Some recommendations that focus on specific outcomes such as prevention of falls and fractures and in which even higher doses of vitamin D are recommended (for example, the American Endocrine Society,[138] Osteoporosis Canada[139]) seem actually to be contradicted by the evidence, which shows no consistent beneficial effects in randomised trials. Our overview of the evidence on vitamin D suggests that strong recommendations cannot be made regarding its supplementation.

Conclusions, unanswered questions, and future research

In conclusion, although vitamin D has been extensively studied in relation to a range of outcomes and some indications exist that low plasma vitamin D concentrations might be linked to several diseases, firm universal conclusions about its benefits cannot be drawn. Observational studies have identified links

with several diseases, but these have either not been evaluated or not been replicated in randomised controlled trials. Randomised controlled trials for autoimmune and cancer related outcomes are clearly lacking. In addition, earlier evidence from randomised controlled trials that vitamin D supplementation (with or without calcium) increases bone mineral density and reduces the risk of fractures in older people is not seen in clinical trials that examine vitamin D only supplementation. On the basis of the results of this review, an association between vitamin D concentrations and birth weight, dental caries in children, maternal vitamin D concentrations at term, and parathyroid hormone concentrations in patients with chronic kidney disease requiring dialysis is probable, but further studies and better designed trials are needed to draw firmer conclusions.

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What is already known on this topic

The role of vitamin D has been explored both in a large number of observational studies and randomised controlled trials and in relation to a multitude of health outcomes

The composite literature is often confusing and has led to heated debates about the role of vitamin D, the optimal concentrations, and related guidelines for supplementation

Recent reports have highlighted the lack of concordance between observational studies and randomised controlled trials, concluding that vitamin D is more likely to be a correlate marker of overall health and not causally involved in disease

What this study adds

This umbrella review collectively presents the evidence from systematic reviews and meta-analyses of observational studies and randomised controlled trials in relation to 137 different outcomes covering a wide range of diseases

An association between vitamin D concentrations and birth weight, dental caries in children, maternal vitamin D concentrations at term, and parathyroid hormone concentrations in chronic kidney disease patients requiring dialysis is probable

In contrast to previous reports, the findings cast doubt on the effectiveness of vitamin D only supplementation for prevention of osteoporosis or falls

This review highlights the absence of meta-analyses in relation to autoimmune disease and the absence of meta-analyses of randomised clinical trials of vitamin D supplementation in respect of cancer, cognitive, and infectious disease outcomes

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Tables

Table 1| Characteristics and main findings of meta-analyses of observational studies reporting unique cancer and cardiovascular outcomes (direction of comparison is high versus low)

Outcome	Biomarker	Meta-analysis metric	No of studies in each MA	No of events	Total No	Relative risk (95% CI)*	P value	I^2 (95% CI)	Egger test P value
Cancer outcomes									
Aggressive prostate cancer	25OHD	OR	6	871	4524	0.98 (0.84 to 1.15)	0.81	33 (0 to 73)	0.97
Aggressive prostate cancer	1,25(OH)2D	OR	2	696	1488	0.75 (0.48 to 1.17)	0.21	0 (NA)	NA
Breast cancer	25OHD	OR	21	11 771	26 317	0.55 (0.42 to 0.71)	1.0×10^{-5}	88 (83 to 91)	0.06
Breast cancer	1,25(OH)2D	OR	3	1802	3627	0.99 (0.68 to 1.44)	0.96	47 (0 to 84)	0.86
Breast cancer: postmenopausal	25OHD	RR	9	3929	8766	0.99 (0.97 to 1.01)	0.33	0 (0 to 54)	0.92
Breast cancer: premenopausal	25OHD	RR	6	1613	2890	1.01 (0.97 to 1.06)	0.67	37 (0 to 74)	0.76
Colon cancer	25OHD	OR	10	1822	4578	0.78 (0.56 to 1.07)	0.13	50 (0 to 74)	0.15
Colon cancer	1,25(OH)2D	OR	4	No info	No info	0.88 (0.57 to 1.35)	0.57	NA	NA
Colorectal cancer	25OHD	RR	10	2764	6712	0.70 (0.58 to 0.84)	0.0002	0 (0 to 53)	0.40
Colorectal cancer	1,25(OH)2D	OR	4	No info	No info	1.01 (0.59 to 1.73)	0.97	NA	NA
Kidney cancer	25OHD	OR	6	740	1480	1.01 (0.65 to 1.58)	0.97	0 (0 to 61)	0.37
Non-Hodgkin's lymphoma (females)	25OHD	OR	4	18	39	0.81 (0.39 to 1.70)	0.59	0 (0 to 68)	0.56
Non-Hodgkin's lymphoma (males)	25OHD	OR	6	25	65	0.65 (0.35 to 1.23)	0.18	13 (0 to 66)	0.72
Ovarian cancer	25OHD	OR	10	884	2489	0.83 (0.63 to 1.09)	0.18	0 (0 to 53)	0.31
Pancreatic cancer	25OHD	OR	6	866	2113	2.13 (1.02 to 4.47)	0.04	17 (0 to 67)	0.90
Prostate cancer	1,25(OH)2D	OR	7	1361	3640	0.99 (0.87 to 1.14)	0.89	40 (0 to 74)	0.43
Prostate cancer	25OHD	OR	14	4353	28 988	1.04 (0.98 to 1.09)	0.15	0 (0 to 47)	0.79
Rectal cancer	25OHD	OR	9	868	2050	0.50 (0.29 to 0.88)	0.01	51 (0 to 75)	0.10
Sporadic colorectal adenoma	25OHD	OR	9	2923	6268	0.82 (0.69 to 0.97)	0.02	66 (13 to 82)	0.34
Sporadic colorectal adenoma recurrence	25OHD	OR	3	586	1366	0.87 (0.57 to 1.33)	0.53	55 (0 to 86)	0.35
Cardiovascular outcomes									
Cardiovascular disease (prevalent)	25OHD	OR	16	7600	64 722	0.67 (0.55 to 0.82)	9.7×10^{-5}	74 (54 to 83)	0.51
Cardiovascular disease	25OHD	RR	19	6123	66 488	0.66 (0.57 to 0.77)	1.6×10^{-7}	61 (28 to 75)	0.98
Cardiovascular disease mortality	25OHD	RR	5	2007	24 387	0.55 (0.36 to 0.85)	0.006	81 (40 to 90)	0.09
Hypertension	25OHD	RR	7	4965	48 633	0.70 (0.58 to 0.86)	0.0004	44 (0 to 75)	0.92
Ischaemic heart disease	25OHD	HR	19	8376	82 982	0.72 (0.65 to 0.81)	4.1×10^{-9}	80 (69 to 86)	0.27
Ischaemic stroke (HR)	25OHD	HR	4	1800	26 596	0.66 (0.55 to 0.80)	2.1×10^{-5}	71 (0 to 86)	0.63
Ischaemic stroke (OR)	25OHD	OR	5	844	31 858	0.52 (0.44 to 0.61)	2.3×10^{-14}	0 (0 to 64)	0.97
Stroke	25OHD	RR	7	1214	39 095	0.61 (0.50 to 0.75)	1.8×10^{-6}	0 (0 to 58)	0.94

HR=hazard ratio; MA=meta-analysis; NA=not applicable; OR=odds ratio; RR=relative risk.

P values were estimated using formulas presented in Altman and Bland 2011.[140]

*Effect estimate and 95% CI estimated on basis of random effects model. Reported effect estimates and 95% CI are presented for colon cancer (1,25(OH)2D) and colorectal cancer (1,25(OH)2D).

Table 2| Characteristics and main findings of meta-analyses of observational studies reporting unique cognitive, infectious, metabolic, neonatal/infant/child related, pregnancy related, skeletal, and other outcomes (direction of comparison is high versus low)

Outcome	Biomarker	Meta-analysis metric	Units	No of studies in each MA	No of events	Total No	Relative risk (95% CI)*	P value	I^2 (95% CI)	Egger test P value
Cognitive disorders										
Alzheimer's disease	25OHD	SMD (to OR)	NA	7	357	1005	0.08 (0.01 to 0.63)	0.02	98 (97 to 98)	0.32
Cognition	25OHD	OR	NA	7	1217	9004	0.42 (0.34 to 0.53)	2.2×10^{-13}	56 (0 to 79)	0.16
Depression (case-control studies)	25OHD	OR	NA	9	2051	19 807	0.77 (0.59 to 1.00)	0.05	53 (0 to 76)	0.22
Depression (cohort studies)	25OHD	HR	NA	3	617	8815	0.44 (0.27 to 0.72)	0.001	28 (0 to 80)	0.49
Infectious diseases										
Tuberculosis	25OHD	SMD (to OR)	NA	7	308	534	0.29 (0.19 to 0.46)	2.0×10^{-7}	41 (0 to 74)	0.79
Metabolic disorders										
Body mass index	25OHD	Z score	NA	37	NA	16 525	−0.15 (−0.19 to −0.11)	8.9×10^{-13}	NA	NA
Metabolic syndrome (prevalent)	25OHD	OR	NA	8	2821	31 416	0.49 (0.38 to 0.64)	1.4×10^{-7}	38 (0 to 71)	0.59
Type 2 diabetes	25OHD	OR	NA	16	4877	72 204	0.63 (0.56 to 0.69)	5.0×10^{-17}	1 (0 to 46)	0.58
Type 2 diabetes (prevalent)	25OHD	OR	NA	9	2424	11 892	0.45 (0.25 to 0.82)	0.008	79 (56 to 87)	0.96
Neonatal/infant/child related outcomes										
Birth length	25OHD	WMD	cm	2	NA	840	0.19 (−0.26 to 0.65)	0.41	NA	NA
Birth weight	25OHD	WMD	grams	4	NA	5541	130.9 (75.1 to 186.7)	5.5×10^{-6}	NA	NA
Head circumference	25OHD	WMD	cm	2	NA	840	0.05 (−0.24 to 0.34)	0.76	NA	NA
Small for gestational age	25OHD	OR	NA	6	NA	6851	0.54 (0.44 to 0.67)	1.8×10^{-8}	8 (0 to 64)	0.81
Pregnancy related outcomes										
Gestational diabetes	25OHD	OR	NA	10	687	4112	0.67 (0.53 to 0.85)	0.0009	0 (0 to 53)	0.58
Pre-eclampsia	25OHD	OR	NA	9	393	3230	0.56 (0.39 to 0.8)	0.002	0 (0 to 58)	0.96
Skeletal outcomes										
Fractures	25OHD	SMD (to OR)	NA	28	1572	2956	0.31 (0.23 to 0.42)	1.3×10^{-13}	77 (66 to 83)	0.78
Hip fracture (hospital based controls)	25OHD	log ratio of geometric mean	nmol/L	8	1116	2201	−0.26 (−0.33 to −0.23)	NA	NA	NA
Hip fracture (population based controls)	25OHD	log ratio of geometric mean	nmol/L	9	818	1655	−0.51 (−0.64 to −0.38)	NA	NA	NA
Other outcomes										
All cause mortality (in CKD patients)	25OHD	RR	NA	10	2110	6853	0.86 (0.81 to 0.92)	4.6×10^{-6}	31 (0 to 66)	0.09
All cause mortality	25OHD	HR	NA	18	15 447	77 155	0.72 (0.66 to 0.78)	2.9×10^{-13}	82 (72 to 87)	0.29

CKD=chronic kidney disease; HR=hazard ratio; MA=meta-analysis; NA=not applicable; OR=odds ratio; RR=relative risk; SMD=standardised mean difference; WMD=weighted mean difference.

P values were estimated using formulas presented in Altman and Bland 2011.[140]

*Effect estimate and 95% CI estimated based on random effects model. Reported effect estimates and 95% CI are presented for hip fracture (population based controls), hip fracture (hospital based controls), birth length, head circumference, and birth weight.

Table 3| General characteristics of non-overlapping meta-analyses of randomised controlled trials of vitamin D supplementation for cardiovascular, metabolic, neonatal/infant/child related, pregnancy related, and other outcomes

Outcome	Population	Type of metric (summary effect)	Units	MA model	No of studies in each MA	Reported summary effect (95% CI)	P value
Cardiovascular outcomes							
Cardiovascular disease	General	RR	NA	Fixed	2	0.95 (0.86 to 1.05)	0.32
Diastolic blood pressure	Normotensive or hypertensive	WMD	mm Hg	No info	3	−0.03 (−1.98 to 1.92)	0.98
Systolic blood pressure	Normotensive or hypertensive	WMD	mm Hg	No info	3	−2.39 (−5.7 to 0.9)	0.16
Metabolic disorders							
Fasting glucose	Diabetes patients with normal glucose tolerance	WMD	nmol/L	No info	No info	0.01 (−0.21 to 0.23)	0.94
Fasting glucose	Diabetes patients with abnormal glucose tolerance	WMD	nmol/L	No info	No info	−0.3 (−0.9 to 0.3)	0.33
High density lipoprotein	General	WMD	mg/dL	Fixed	8	−0.14 (−0.99 to 0.71)	0.76
Insulin resistance	Diabetes	SMD	NA	No info	5	0.16 (−0.11 to 0.42)	0.24
Total cholesterol	General	WMD	mg/dL	Fixed	11	1.52 (−1.42 to 4.46)	0.32
Low density lipoprotein	General	WMD	mg/dL	Fixed	7	3.23 (0.55 to 5.9)	0.02
Triglycerides	General	WMD	mg/dL	Fixed	8	−1.92 (−7.72 to 3.88)	0.53
Neonatal/infant/child related outcomes							
Birth length	Pregnant women	WMD	cm	Random	2	0.97 (−0.41 to 2.34)	0.17
Low birth weight	Pregnant women	RR	NA	Fixed	3	0.4 (0.23 to 0.71)	0.001
Dental caries	Children	RR	NA	Random	38	0.53 (0.43 to 0.65)	3.7×10^{-9}
Head circumference at birth	Pregnant women	WMD	cm	Random	2	0.43 (0.06 to 0.79)	0.02
Small for gestational age	Pregnant women	RR	NA	Fixed	2	0.67 (0.40 to 1.11)	0.12
Pregnancy related outcomes							
Maternal vitamin D concentrations at term	Pregnant women	WMD	nmol/L	Random	4	47.08 (23.76 to 70.39)	8.7×10^{-5}
Mean gestational age at delivery	Pregnant women	WMD	Weeks	Fixed	2	0.17 (-0.16 to 0.51)	0.32
Preterm delivery	Pregnant women	RR	NA	Fixed	2	0.77 (0.35 to 1.66)	0.52
Other outcomes							
Alkaline phosphatase	CKD NRD	WMD	U/L	Fixed	2	−21.81 (−40.39 to 3.22)	0.06
Alkaline phosphatase	CKD RD	WMD	U/L	Fixed	3	−27.35 (−50.69 to −4.01)	0.02
Creatinine clearance	CKD NRD	WMD	mL/min	Fixed	4	−1.68 (−6.92 to 3.56)	0.54
Mortality	General (vitamin D_3)	RR	NA	Random	9	0.91 (0.82 to 1.02)	0.09
Mortality	General (vitamin D_2)	RR	NA	Random	8	1.04 (0.97 to 1.11)	0.26
Mortality	CKD NRD	RR	NA	Fixed	4	1.40 (0.38 to 5.15)	0.63
Mortality	CKD RD	RR	NA	Fixed	5	1.34 (0.34 to 5.24)	0.69
Parathyroid hormone	CKD NRD	WMD	pmol/L	Fixed	4	−49.34 (−85.70 to −12.97)	0.008
Parathyroid hormone	CKD RD	WMD	pmol/L	Fixed	6	−196.05 (−298.43 to −93.66)	0.0002
Parathyroidectomy	CKD RD	RR	NA	Fixed	2	0.82 (0.05 to 12.47)	0.90
Risk of hypercalcaemia	CKD NRD	RR	NA	Fixed	7	3.04 (1.17 to 7.90)	0.02
Risk of hypercalcaemia	CKD RD	RR	NA	Fixed	5	3.80 (0.90 to 16.12)	0.07
Risk of hyperphosphataemia	CKD NRD	RR	NA	Fixed	2	1.58 (0.47 to 5.30)	0.47
Risk of hyperphosphataemia	CKD RD	RR	NA	Fixed	2	1.57 (0.97 to 2.54)	0.07
Risk of requiring dialysis	CKD NRD	RR	NA	Fixed	4	0.76 (0.36 to 1.62)	0.48
Subperiosteal erosions	CKD RD	RR	NA	Fixed	3	0.41 (0.07 to 2.38)	0.33
Vascular calcification	CKD RD	RR	NA	Fixed	2	1.09 (0.45 to 2.67)	0.86

Table 3 (continued)

Outcome	Population	Type of metric (summary effect)	Units	MA model	No of studies in each MA	Reported summary effect (95% CI)	P value

CKD NRD=chronic kidney disease not requiring dialysis; CKD RD=chronic kidney disease requiring dialysis; RR=relative risk; SMD=standardised mean difference; WMD=weighted mean difference.

P values were estimated using formulas presented in Altman and Bland 2011.[140]

Table 4| General characteristics of non-overlapping meta-analyses of randomised controlled trials of vitamin D supplementation for skeletal outcomes

Skeletal outcome	Population	Type of metric (summary effect)	Units	MA model	No of studies in each MA	Reported summary effect (95% CI)	P value
Bone mineral density	Healthy children	SMD	% change	Fixed	5	0.1 (–0.06 to 0.26)	0.22
Bone mineral density	Community dwelling adults	WMD	% change	Random	3	–0.9 (–2.10 to 0.40)	0.16
Bone mineral density in femoral neck	Community dwelling adults	WMD	% change	Random	8	1.10 (0.40 to 1.90)	0.004
Bone mineral density in forearm	Community dwelling adults	WMD	% change	Random	2	–0.70 (1.70 to 0.40)	0.19
Bone mineral density in forearm	Healthy children	SMD	% change	Random	3	0.04 (–0.36 to 0.45)	0.86
Bone mineral density in hip	Healthy children	SMD	% change	Random	4	0.06 (–0.18 to 0.29)	0.63
Bone mineral density in hip	Community dwelling adults	WMD	% change	Random	6	0.70 (–0.10 to 1.60)	0.11
Bone mineral density in lumbar spine	Healthy children	SMD	% change	Fixed	5	0.15 (–0.01 to 0.31)	0.07
Bone mineral density in lumbar spine	Community dwelling adults	WMD	% change	Random	7	0.10 (–0.60 to 0.70)	0.78
Bone pain	CKD RD	RR	NA	Fixed	4	0.29 (0.03 to 2.63)	0.28
Falls	Older adults	OR	NA	Random	10	0.97 (0.84 to 1.11)	0.68
Falls: rate of falls	Older people in care facilities or hospitals	RaR	NA	Random	2	0.55 (0.19 to 1.64)	0.28
Falls: rate of falls	Older people in community	RaR	NA	Random	2	1.14 (1.03 to 1.27)	0.01
Fractures	Men aged >65 years and postmenopausal women	RR	NA	Fixed	10	1.01 (0.93 to 1.09)	0.82
Fractures	CKD RD	RR	NA	Fixed	4	1.00 (0.06 to 15.41)	1.00
Fractures: hip	Men aged >65 years and postmenopausal women	RR	NA	Fixed	9	1.15 (0.99 to 1.33)	0.06
Fractures: non-vertebral	People aged >65 years	RR	NA	No info	5	0.79 (0.63 to 0.99)	0.04
Fractures: non-vertebral, non-hip	Older women	OR	NA	Random	2	0.69 (0.21 to 1.66)	0.49
Fractures: vertebral or deformity	Men aged >65 years and postmenopausal women	RR	NA	Random	5	0.90 (0.42 to 1.92)	0.80
Performance measures: balance sway	Older adults	SMD	NA	Fixed	3	–0.20 (–0.39 to –0.01)	0.04
Performance measures: lower extremity strength	Older adults	SMD	NA	Fixed	3	0.05 (–0.11 to 0.20)	0.54
Performance measures: muscle strength	Older adults	SMD	NA	Fixed	3	–0.19 (–0.35 to –0.02)	0.02

CKD RD=chronic kidney disease requiring dialysis; OR=odds ratio; RaR=rate ratio; RR=relative risk; SMD=standardised mean difference; WMD=weighted mean difference.

P values were estimated using formulas presented in Altman and Bland 2011.[140]

Table 5| Overlap between meta-analyses of observational studies and vitamin D supplementation randomised controlled trials

	Observational		Randomised controlled trials			CI excluded null	
Disease outcome	Metric	Effect size (95% CI)	Metric	Effect size (95% CI)	Concordant direction	Both	Observational only
Cardiovascular disease[102 130]	OR	0.66 (0.57 to 0.77)	OR	0.95 (0.86 to 1.05)	Yes	No	Yes
Hypertension/blood pressure[104 127]	OR	0.70 (0.58 to 0.86)	WMD	−2.39 (−5.7 to 1.92)	Yes	No	Yes
Birth weight/ risk of low birth weight[36 61]	WMD	130.9 (75.1 to 186.7)	OR	0.4 (0.23 to 0.71)	Yes	Yes	No
Birth length[36 112]	WMD	0.19 (−0.26 to0.65)	WMD	0.97 (−0.41 to 2.34)	Yes	No	No
Head circumference[36 112]	WMD	0.05 (−0.24 to 0.34)	WMD	0.43 (0.06 to 0.79)	Yes	No	No
Small for gestational age[36 61]	OR	0.54 (0.44 to 0.67)	OR	0.67 (0.4 to 1.11)	Yes	No	Yes
Mortality in CKD patients[84 120]	OR	0.86 (0.81 to 0.92)	OR	1.4 (0.38 to 5.15)	No	No	Yes
All cause mortality[66 110]	OR	0.72 (0.66 to 0.78)	OR	0.91 (0.82 to 1.02)	Yes	No	Yes
Fractures in older populations[91 107]	OR	0.31 (0.23 to 0.42)	OR	1.01 (0.93 to 1.09)	No	No	Yes
Hip fracture[37 107]	Log ratio of geometric mean	−0.26 (−0.33 to −0.23)	OR	1.15 (0.99 to 1.33)	No	No	Yes

CI=confidence interval; CKD=chronic kidney disease; OR=odds ratio; WMD=weighted mean difference.

Table 6| Evidence of relation between high vitamin D concentrations or vitamin D supplementation and clinical outcomes

Evidence category*	Health benefits	Heath risks
Convincing	None	None
Probable	Decreases risk of dental caries in children	None
	Increases levels of birth weight and maternal vitamin D concentrations at term	
	Decreases levels of parathyroid hormone concentrations in CKD RD	
Suggestive	Decreases risk of colorectal cancer, non-vertebral fractures, CVD, CVD prevalence, hypertension, ischaemic stroke, stroke, cognition, depression (cohort studies), body mass index, metabolic syndrome prevalence, type 2 diabetes, small for gestational age birth, gestational diabetes mellitus	Increases rate of falls (community) and risk of hypercalcaemia in CKD NRD
	Decreases levels of balance sway, alkaline phosphatase concentrations in CKD RD, parathyroid hormone concentrations in CKD NRD	
	Increases levels of head circumference at birth, LDL, bone mineral density in femoral neck, muscle strength	
No conclusion	Decreases risk of ankylosing spondylitis, Crohn's disease, multiple sclerosis, osteoarthritis, rheumatoid arthritis, rheumatoid arthritis activity, scleroderma, systemic lupus erythematosus, thyroid autoimmunity, type 1 diabetes, type 1 diabetes in childhood (maternal vitamin D status), vitiligo, breast cancer, breast cancer prognosis, colon cancer, colorectal adenoma, colorectal adenoma recurrence, colorectal cancer prognosis, lung cancer, melanoma prognosis, non-Hodgkin's lymphoma, non-small cell lung cancer prognosis, oesophageal cancer, ovarian cancer, prostate cancer prognosis, rectal cancer, renal cancer, stomach cancer, CVD in ethnic minorities, CVD mortality, hypertension in children, ischaemic heart disease, myocardial infarction, Alzheimer's disease, depression (case-control studies), active tuberculosis, acute respiratory infection, infectious disease mortality, metabolic syndrome in ethnic minorities, obesity in ethnic minorities, type 2 diabetes in ethnic minorities, type 2 diabetes prevalence, allergic rhinitis and atopic dermatitis/eczema (maternal vitamin D status), cerebral function and diseases (maternal vitamin D status), childhood infections (maternal vitamin D status), wheezing and asthma in childhood (maternal vitamin D status), bacterial vaginosis in pregnant women, fertility, postpartum depression, pre-eclampsia in pregnant women, pregnancy associated breast cancer, bone health in pregnant and lactating women, bone pain in CKD RD, falls, rate of falls (care facilities), fractures in older people, fractures in CKD RD, hip fractures, non-vertebral non-hip fractures, vertebral fractures or deformity, performance measures in older people, rickets in children, all cause mortality, mortality in CKD, risk of requiring dialysis in CKD NRD, parathyroidectomy in CKD RD, subperiosteal erosions in CKD RD, mammographic breast density	Increases risk of pancreatic cancer, hyperphosphataemia in CKD, vascular calcification in CKD RD, hypercalcaemia in CKD RD
	Decreases levels of HDL in children, LDL in children, triglycerides in children, insulin/glucose metabolism in children, triglycerides, insulin resistance of diabetes patients, bone mineral density, bone mineral density in forearm, alkaline phosphatase concentrations in CKD NRD, creatinine clearance in CKD	
	Increases levels of total cholesterol concentrations, neonatal and infant growth, length of gestation, bone mineral content in infants, bone mineral density in hip, bone mineral density in lumbar spine (children)	
Substantial effect unlikely	Decreases risk of aggressive prostate cancer, premenopausal breast cancer, postmenopausal breast cancer, cancer mortality, kidney cancer, prostate cancer, caesarean section	None
	Decreases levels of fasting glucose in diabetes patients, HDL, adiposity in children (maternal vitamin D status)	
	Increases levels of birth length (maternal vitamin D status), bone mineral density in children, bone mineral density in forearm in children, bone mineral density in hip in children, bone mineral density in lumbar spine, lower extremity strength	

CKD=chronic kidney disease; CVD=cardiovascular disease; HDL=high density lipoprotein; LDL=low density lipoprotein; NRD=not requiring dialysis; RD=requiring dialysis.

*See box.

Figures

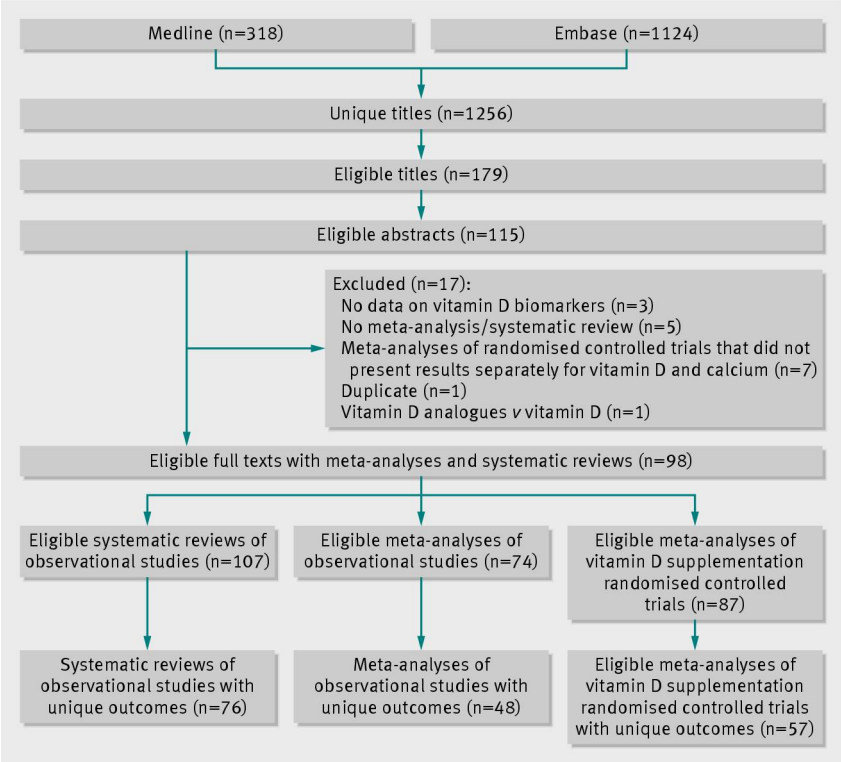

Fig 1 Flow chart of eligible studies

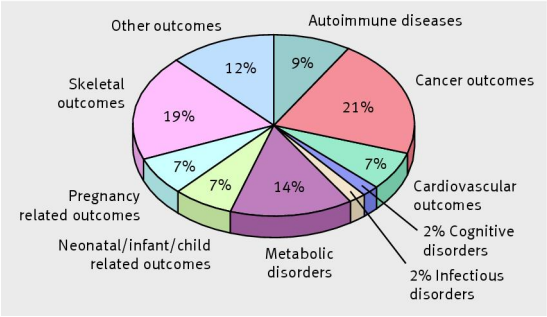

Fig 2 Map of 137 vitamin D related outcomes: percentage of outcomes per outcome category for all study designs

Outcome	No of events/ total	No of studies	Comparison	Relative risk (95% CI)
25OHD				
Aggressive prostate cancer[76]	871/4524	6	Per 10 ng/mL	0.98 (0.84 to 1.15)
Breast cancer[101]	11 771/26 317	21	Quarters	0.55 (0.42 to 0.71)
Postmenopausal breast cancer[105]	3929/8766	9	Per 5 ng/mL	0.99 (0.97 to 1.01)
Pre-menopausal breast cancer[105]	1613/2890	6	Per 5 ng/mL	1.01 (0.97 to 1.06)
Colon cancer[35]	1822/4578	10	Categories	0.78 (0.56 to 1.07)
Colorectal cancer[79]	2764/6712	10	Categories	0.70 (0.58 to 0.84)
Kidney cancer[74]	740/1480	6	≥75 v 50-75 nmol/L	1.01 (0.65 to 1.58)
Non-Hodgkin's lymphoma[86]	18/39	4	>100 v 50-75 nmol/L	0.81 (0.39 to 1.70)
Non-Hodgkin's lymphoma[86]	25/65	6	>100 v 50-75 nmol/L	0.65 (0.35 to 1.23)
Ovarian cancer[96]	884/2489	10	Per 20 ng/mL	0.83 (0.63 to 1.09)
Pancreatic cancer[88]	866/2113	6	>100 v 50-75 nmol/L	2.13 (1.02 to 4.47)
Prostate cancer[76]	4353/28 988	14	Per 10 ng/mL	1.04 (0.98 to 1.09)
Rectal cancer[35]	868/2050	9	Categories	0.50 (0.29 to 0.88)
Sporadic cancer[95]	2923/6268	9	Per 20 ng/mL	0.82 (0.69 to 0.97)
Sporadic cancer recurrence[95]	586/1366	3	Per 20 ng/mL	0.87 (0.57 to 1.33)
Cardiovascular disease[102]	6123/66 488	19	Categories	0.66 (0.57 to 0.77)
Cardiovascular disease (prevalent)[83]	—/64 722	16	Categories	0.67 (0.55 to 0.82)
Cardiovascular disease mortality[78]	2007/24 387	5	Categories	0.55 (0.36 to 0.85)
Hypertension[104]	4965/48 633	7	Categories	0.70 (0.58 to 0.86)
Ischaemic heart disease[66]	8376/82 982	19	Quarters	0.72 (0.65 to 0.81)
Ischaemic stroke (hazard ratio)[100]	1800/26 596	4	Quarters	0.66 (0.55 to 0.80)
Ischaemic stroke (odds ratio)[100]	844/31 858	5	Quarters	0.52 (0.44 to 0.61)
Stroke[89]	1214/39 095	7	Categories	0.61 (0.50 to 0.75)
Alzheimer's disease[99]	357/1005	7	Per SD	0.08 (0.01 to 0.63)
Cognition[71]	1217/9004	7	Quarters	0.42 (0.34 to 0.53)
Depression[98]	2051/19 807	9	<50 v > 50 nmol/L	0.77 (0.59 to 1.00)
Depression[98]	617/8815	3	<50 v >50 nmol/L	0.44 (0.27 to 0.72)
Tuberculosis[82]	308/534	7	Per SD	0.29 (0.19 to 0.46)
Metabolic syndrome (prevalent)[83]	—/31 416	8	Categories	0.49 (0.38 to 0.64)
Type 2 diabetes[103]	4877/72 204	16	Categories	0.63 (0.56 to 0.69)
Type 2 diabetes (prevalent)[83]	—/11 892	9	Categories	0.45 (0.25 to 0.82)
Small for gestational age[36]	—/6851	6	Categories	0.54 (0.44 to 0.67)
Gestational diabetes[36]	687/4112	10	Categories	0.67 (0.53 to 0.85)
Pre-eclampsia[36]	393/3230	9	Categories	0.56 (0.39 to 0.80)
Fractures[91]	1572/2956	28	Per SD	0.31 (0.23 to 0.42)
Mortality in chronic kidney disease patients[84]	2110/6853	10	Per 10 ng/mL	0.86 (0.81 to 0.92)
All cause mortality[66]	15 447/77 155	18	Quarters	0.72 (0.66 to 0.78)
1,25(OH)2D				
Aggressive prostate cancer[76]	696/1488	2	Per 10 ng/mL	0.75 (0.48 to 1.17)
Breast cancer[68]	1802/3627	3	Categories	0.99 (0.68 to 1.44)
Colon cancer[35]	—/—	4	Categories	0.88 (0.57 to 1.35)
Colorectal cancer[35]	—/—	4	Categories	1.01 (0.59 to 1.73)
Prostate cancer[76]	1361/3640	7	Per 10 ng/mL	0.99 (0.87 to 1.14)

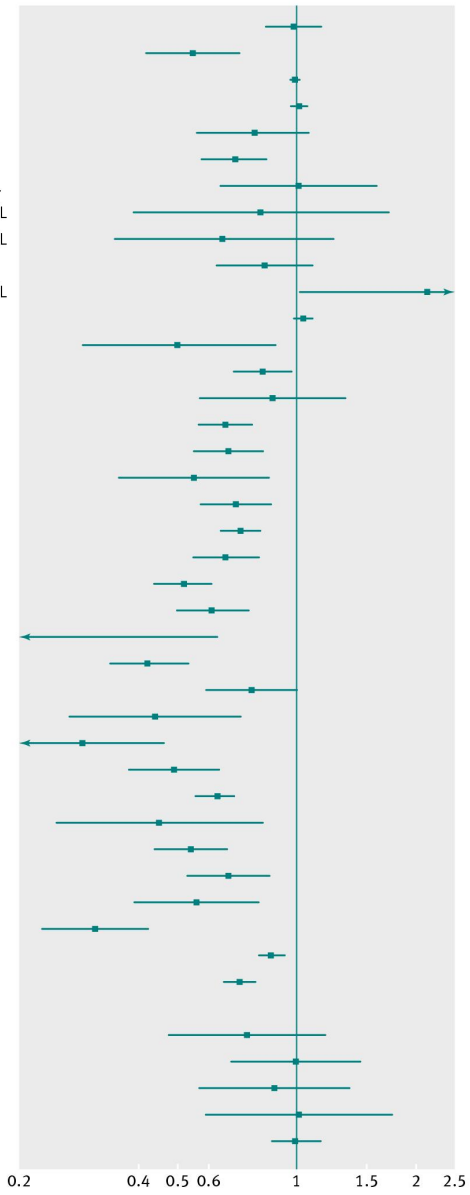

Fig 3 Forest plot of all meta-analyses of observational studies stratified by measured biomarker with relative risk as type of metric

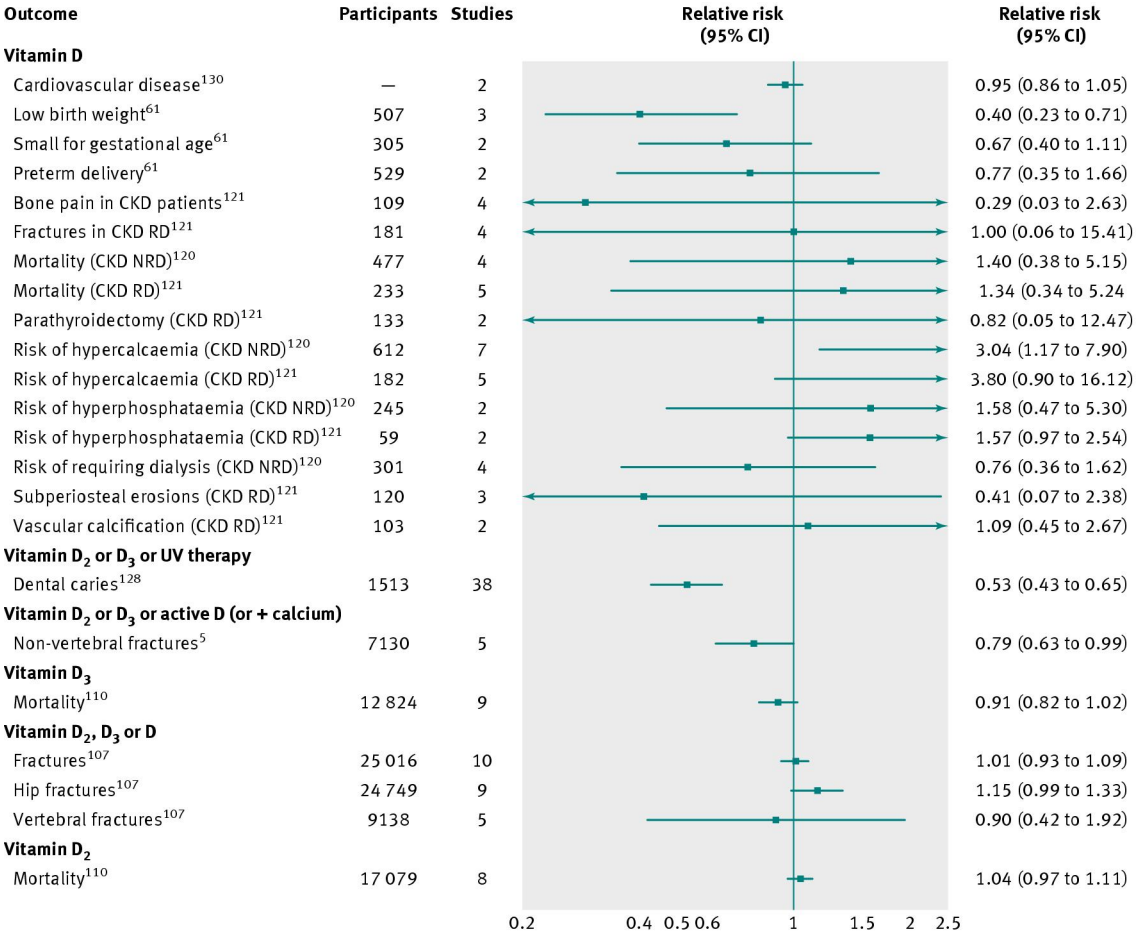

Fig 4 Forest plot of all meta-analyses of randomised controlled trials with relative risk as type of metric by compound administered. CKD=chronic kidney disease patients; NRD=not requiring dialysis; RD=requiring dialysis; UV=ultraviolet